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P/546-279 REISSUE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Patent Application of:
William STERN

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For: NASAL CALCITONIN FORMULATION

Confirmation No.: 8408

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Examiner: Mina Haghighatian

Mail Stop Reissue
Commissioner for Patents
P.O. Box 1450
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SECOND DECLARATION OF INVENTOR
WILLIAM STERN UNDER 37 CFR §1.132

I, William Stern, hereby declare that:

1. I am the inventor named in the above-identified patent application, and am familiar with its contents. I have also reviewed the prior art cited by the Examiner in the most recent Office Action and am familiar with that prior art.

2. Since 2006, I have held the position of Principal Scientist-I in the Formulation Development Group at Unigene Laboratories, Inc., located in Fairfield, New Jersey (Unigene). Unigene is the owner of the above-identified patent application, and of related original U.S. patent 6,440,392. Prior to assuming my present position at Unigene, I was a Senior Research Scientist in Unigene's Protein Chemistry Group. Prior to that, I was a Senior Scientist in Unigene's Protein Chemistry Group. I have been with Unigene since 1986.

3. I received a Ph.D. in Biological Chemistry from the University of Michigan in 1972.

NEW MATTER ISSUES

4. I have reviewed Tables 1 and 3 in columns 5 and 6 of original U.S. Patent 6,440,392 (and revised Tables 1 and 3, revised to correct inadvertent errors, discussed *infra)*. The data set forth in those tables was produced by me and by others working under my supervision. In each of the experiments giving rise to the data in Tables 1 and 3, citric acid was buffered at a pH of at least 3.7, specifically 3.7 in Table 1 and 3.8 in Table 2 (See the parenthetical at the top of the first column of both Table 1 and Table 3, as amended in the accompanying amendment).

5. Citric acid buffered at pH 3.7 or 3.8, at all of the citric acid concentrations of 10 mM or higher shown in Tables 1 and 3, is necessarily a combination of citric acid and citric acid salt, as dictated by a version of the Henderson-Hasselbach equation for buffers with two pK's as noted below:

$$pH = ((pK1 + pK2) + \log (salt/acid))/2$$

In all of the concentrations of citric acid reported in Tables 1 and 3 that are 10mM or higher, the pH would have been considerably lower than 3.7 if the citric acid had not been buffered by the presence of a salt. For example, had the pH been raised to 3.7 or higher by a mere addition of water, the resulting citric acid concentration would be significantly below 10mM. The Henderson-Hasselbach equation dictates that the 10mM (or higher) aqueous citric acid solution of Tables 1 and 3 exists as a mixture of citric acid and citric acid salt at a pH of 3.7 or higher. This does not necessarily mean that salt has been added. A base could be used to raise pH to 3.7 or higher. However, the addition of a base would cause the formation of salt in accordance with the above Henderson-Hasselbach equation. In other words, regardless of whether pH is raised to 3.7 or higher by using a base, or by using a salt, salt will necessarily be present either (1) because salt was included during preparation, or (2) because salt was formed when base was included during preparation.

6. In view of the foregoing, the effect on bioavailability and stability that is reported in Tables 1 and 3 of U.S. Patent 6,440,392, respectively, is provided in solutions that

necessarily include a combination of both citric acid and citric acid salt. This is true not only of original Tables 1 and 3, but also of revised Tables 1 and 3 discussed *infra*.

GREBOW PRIOR ART

7. I have reviewed the Grebow reference cited by the Examiner in the most recent Office Action, including the paragraph at column 11, lines 35-47 which, for convenience, is reproduced below:

> "Preferably, the subject calcitonin is formulated in water or a pharmaceutically acceptable aerosol composition. Nasal spray solutions are especially preferred with water or in buffer at a ph [sic] of between about 3.0 to 8.0, using a pharmaceutically acceptable buffer system. The buffer system of the present invention preferably contain [sic] a sodium or potassium phosphate/phosphoric acid buffer or a sodium or potassium acetate/acetic acid buffer or a sodium or potassium citrate/citric acid buffer in the range of 0.01 M to 0.5 M and preferably in the range of 0.05M to 0.2M. This concentration was found effective to provide stability of the dissolved calcitonin in the diluent base or vehicle." (Emphasis added)

8. On information and belief, the statement in the above-quoted Grebow excerpt that "[t]his concentration was found effective to provide stability of the dissolved calcitonin in the diluent base or vehicle." does not refer to shelf stability of a pharmaceutical product (as tested in Table 3 of the present patent application). When the Grebow statement about stability is read in context of the paragraph in which it appears, and in context of the overall Grebow patent, it clearly appears that this sentence refers instead either to pH stability, or to short-term stability while the bioavailability testing proceeds per Grebow columns 14-15. In the above-quoted Grebow excerpt, the discussion preceding the statement about stability is a discussion of various buffer systems for maintaining pH within Grebow's desired 3.0-8.0 range. In context, I believe that the statement about stability simply means that the buffer systems that were discussed in that paragraph assured that there was no reason to worry about pH drift, or pH-related instability (*e.g.*, caused by pH going outside of Grebow's preferred 3.0-8.0 range). There is nothing in the above-quoted paragraph, or elsewhere in the Grebow reference, that leads me to believe that Grebow et al. tested their formulations for shelf stability, as was the purpose of the testing reported in Table 3 of the present patent application. For all of the foregoing reasons, I do

not believe that the Grebow reference discloses or suggests that citric acid or citric acid salt has an effect on shelf stability of nasal calcitonin solutions, or that Grebow et al. expected any such effect.

9. In my opinion, the Grebow reference also fails to disclose or suggest that citric acid or citric acid salt has an effect on bioavailability. The Grebow reference instead uses aminolevulinic acid for that purpose. See the Grebow reference's bioavailability testing at columns 14-15, using pharmaceutical formulations that do not have any citric acid or citric acid salt.

10. In my opinion, the Grebow reference discusses citric acid and citric acid salt only as buffers for maintaining pH within desired ranges, and teaches that other buffers, which do not even use citric acid or citric acid salt, are equally useful. See, for example, Grebow at column 11, lines 40-42. See also the formulations Grebow actually tested for bioavailability at columns 14-15, which were free of citric acid or citric acid salt.

11. In my opinion, none of the references cited by the Examiner in the most recent Office Action, disclose or suggest that shelf stability of a nasal calcitonin formulation can be adversely affected by raising the concentration of citric acid or citric acid salt, independent of any pH effects.

12. Attached as Exhibit A hereto is a study by an outside contractor which was performed for Unigene, in 2001, for the purpose of providing Unigene with a better understanding of a mechanism of calcitonin loss over time in nasal calcitonin formulations of the present invention. The report shows a reaction of the citrate anion with the calcitonin active agent to undesirably form an adduct. While this study was not conducted under the conditions set forth in Table 3, or at citric acid (and/or citric acid salt) levels in excess of 50 mM, I believe it likely that the undesirable reaction reported in this study is involved in the unexpected drop in shelf stability that Table 3 reports at citric acid (and/or citric acid salt) concentrations higher than 50 mM. While there are degradation products other than the adduct, the adduct was identified as the most significant degradation product (see p7-8 of exhibit A).

13. In my opinion, neither the Grebow reference, nor the other prior art cited

in the most recent Office Action, predicted either the adduct formation referenced in the prior paragraph (and in Exhibit A), or any other pH-independent decrease in shelf stability as a function of citric acid and/or citric acid salt concentration, as taught by the present patent application. One reason supporting my belief that Grebow did not expect this is the above-quoted paragraph from the Grebow reference which specifically suggests using buffer, whether citric acid or another buffer, at concentrations from 50 to 200 mM (see column 11, lines 44-45 of Grebow). I do not believe the Grebow reference would have recommended concentrations above 50 mM in that manner had Grebow et al. expected the problem of adduct formation (or significant shelf-stability loss by any other mechanism) as concentrations of citric acid and/or citric acid salt increase, especially as they increase beyond 50 mM. It is believed that these unexpected effects on shelf stability are not disclosed or suggested in the Examiner's cited prior art.

CHIODINI PRIOR ART

14. I have calculated the osmotic pressure of example 19 of the Chiodini patent that the Examiner has cited in the most recent Office Action. The calculation assumes that mOsmol/L of the overall composition is equal to the sum of mOsmol/L for each component of the composition where mOsmol/L is equal to grams per liter of each such component multiplied by moles per gram multiplied by osmolarity per mole multiplied by 1,000 mOsmol/osmol. Based on this calculation, I believe that the osmotic pressure of example 19 of Chiodini is at least 441 mOsmol/L. On information and belief, the fact that example 19 of Chiodini contains 11% PEG 600 significantly contributes to the osmotic pressure of Chiodini's example 19 being higher than the range (250-350 mOsmol/L), recited in some of the presently-pending claims that directly or indirectly recite osmotic pressure.

ADDITIONAL DATA AND CLARIFICATIONS

15. The specification revision at Column 5, line19 that maximum rsCT levels were "usually" detected at t=120 minutes is supported by records kept by Unigene in the ordinary course of business, indicating that while maximum levels were usually detected at t=120, they were on some occasions detected at other points in time. The maximum levels reported in Table 1 are the maximums without regard to the time at which the maximum occurred. Likewise, records kept by Unigene in the ordinary course of business support the corrections in Column 6, lines 1-4 that phenyl ethyl alcohol was present at 0.2% and sodium

chloride at 0.85%. Such records also support correcting the pH at Column 6, line 4 from 3.7 to 3.8. Other corrections are discussed in more detail *infra*.

16. Attached as Exhibit B hereto is a revised Table 1 (and comparison to original Table 1) , revised to show the mean and standard deviation of the reported parameter if calculated with all of the experiments that were available for inclusion at the time that the priority application was filed (with the exception of one or more experiments that differed by the inclusion of dimyristoylphophatidylglycerol, hereinafter "DMPG"). Experiment(s) that included DMPG are excluded because of the possibility that any observed differences in bioavailability might be attributable, at least in part, to the DMPG, thus limiting these experiment(s)' value as data point(s) in the universe summarized by Table 1. The data from the DMPG experiment(s) can be made available to the Examiner, should the Examiner so request. It is my opinion that the revised Table 1 set forth in Exhibit B does not alter the primary conclusions to be drawn from Table 1 as originally presented -- namely, (1) that citric acid (and/or citric acid salt) is beneficial to bioavailability of a nasal calcitonin formulation, and (2) that increasing the concentration of citric acid and/or citric acid salt is also beneficial to bioavailability. Table 1 (original and revised) continues to show that this desirable effect on bioavailability is independent of pH effects - - pH having been held constant as citrate was varied.

17. Attached as Exhibit C are summaries of records kept by Unigene in the ordinary course of business documenting the basis for revised Table 1.

18. Attached as Exhibit D hereto is a revised Table 3 (and for comparison purposes, original Table 3). An inadvertent error during automated data analysis resulted in an incorrect number being entered for percent sCT recovered in the last row and last column of original Table 3. While the new number shows a lesser loss of sCT than was originally reported, revised Table 3 continues to show that shelf stability of the nasal calcitonin formulation is reduced, independent of any pH effects, by increasing the concentration of citric acid and/or citric acid salt beyond certain low levels. Like Table 1, Table 3 also shows the effects of varying the citrate concentration, while holding pH constant.

19. Attached as Exhibit E are summaries of records kept by Unigene in the ordinary course of its business documenting the basis for the foregoing correction to Table 3.

20. Attached as Exhibit F is a chart that I have prepared summarizing the results of other studies conducted by, or on behalf of, Unigene, related to shelf stability of nasal calcitonin formulations. These include studies conducted by a third party (MQS) and studies conducted at Unigene's production facility in Boonton, New Jersey. Exhibit F also includes studies conducted at my Fairfield, New Jersey, Research and Development Laboratory, one of which is the study that is reported in Table 3 (Fairfield Study 073099).

21. Attached as Exhibit G hereto is a revised Table 2 (and comparison to original Table 2), revised to show the mean and standard deviation for the bioavailability and Cmax of formulations containing 0.2% phenylethyl alcohol and 0.5% benzyl alcohol. This formulation is the same as that reported in Exhibit B, the revised Table 1, for 0 mM citric acid. The bioavailability and Cmax for 0.2% phenylethyl alcohol and 0.5% benzyl alcohol in revised Table 2 is the same as that for 0 mM citric acid in revised Table 1 and was calculated from data in Exhibit C. It is my opinion that the revised Table 2 set forth in Exhibit G does not alter the primary conclusions to be drawn from Table 2 as originally presented -- namely, that preservatives have no effect on bioavailability or Cmax.

22. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patents issued thereon.

9/7/07
Date

William Stern
William Stern